A STUDY ON THE EFFECTIVENESS OF MONO AND DUAL ANTIPLATELET THERAPY IN SECONDARY PREVENTION OF VASCULAR EVENTS

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DECLARATION

I do hereby declare that the dissertation work entitled **"A STUDY ON THE EFFECTIVENESS OF MONO AND DUAL ANTIPLATELET THERAPY IN SECONDARY PREVENTION OF VASCULAR EVENTS"** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy Practice,** was done by me under the guidance of **Dr. SUCHANDRA SEN, M.PHARM., Ph.D.** at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, during the academic year 2011-2012.

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EVALUATION CERTIFICATE

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Dedicated to God Almighty," the most compassionate the most merciful " , my beloved parents and my sweet niece Fiya ...

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Abbreviations

ABBREVIATIONS

- AAN-American Academy of Neurology
- ACAPS-Asymptomatic Carotid Artery Plaque Study
- ACCP-American College of Chest Physicians
- ADP-Adenosine Diphosphate
- AF- Atrial Fibrillation
- AHA-American Heart Association
- APSAC-Anisolysed Plasminogen Streptokinase Activator Complex
- ASA-Acetyl Salicylic Acid
- ASA-American Stroke Association
- CAPRIE-Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
- CARESS-Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis
- CEA -Carotid Endartectomy
- CI-Confidence Interval
- CLOP-Clopidogrel
- COX-Cyclooxygenase
- CV-Cardiovascular.
- DIP-Dipyridamole
- ECST-European Carotid Surgery Trial
- ESC -European Society of Cardiology
- ESO -European Stroke Organization
- FDA-Food and Drug Administration
- GP-Glycoprotein
- HDL-High Density Lipoprotein

- ICP-Intracranial Pressure
- IHD-Ischemic Heart Disease
- LDL-Low Density Lipoprotein
- LSD-Lysergic Acid Derivative
- MATCH-Management of ATherothrombosis with Clopidogrel in High-risk patients
- MES-Microembolic Signals
- MI-Myocardial Infarction
- NASCET -North American Symptomatic Carotid Endartectomy Trials Collaborates
- NIHSS-National Institutes of Health Stroke Scale
- OR-Odds Ratio
- PCI-Percutaneous Coronary Intervention
- PET-Positron Emission Tomography
- SHEP- Systolic Hypertension in the Elderly Program
- SMR- Standard Mortality Ratios
- STEMI -ST Elevation Myocardial Infarction
- TCD-Transcranial Doppler Ultrasound
- TIC-Ticlopidine
- t-PA- Tissue Plasminogen Activator
- TXA2-Thromboxane A2
- UK-United Kingdom
- US-United States

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Introduction

INTRODUCTION

Stroke or a cerebrovascular accident is the sudden death of brain cells due to the inadequate blood flow. The WHO clinically defines stroke as ' the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin'. Stroke is a clinical syndrome which can be sub divided into two broad categories according to its pathophysiology. Ischaemic strokes which are caused by either cerebral thrombosis or embolism accounting for 50-85% of all strokes worldwide and haemorragic strokes caused by subarachnoid haemorrhage or intracerebral haemorrhage and which account for 1%-7% and 7%-27% respectively of all strokes worldwide. **(Balucani et al., 2010).**

The extent and site of brain injury indicates the effect of stroke but the clinical symptoms alone cannot accurately predict its underlying causes. Stroke symptoms involve speech impairment, memory loss, acute onset of unilateral paralysis, loss of vision, speech impairment, impaired reasoning ability, coma or death. It is found that one third of all strokes are preceded by Transient Ischemic attacks(TIAs), also called mini strokes, which are able to temporarily interrupt blood flow to the brain. **(Balucani et al., 2010).**

The majority of ischemic strokes are found to be of arterial origin such as atherothrombosis — which is a generalized, diffuse and progressive polyvascular disease. In most of acute ischemic strokes, unstable angina, acute MI, sudden cardiac death, and peripheral arterial disease (PAD), atherothrombosis have a key role. **(Balucani et al., 2010).**

The most widely used system of aetiological ischaemic stroke classification is Trial of Org 10172 in Acute Stroke Treatment (TOAST) .The TOAST classification system has five categories: 1) large-artery atherosclerosis 2) cardioembolism 3) small-artery

occlusion (lacune) 4) stroke of other determined etiology and 5) stroke of undetermined etiology. **(Wolf and Hennerici, 2011).**

Antiplatelet therapy remains the cornerstone of therapy for treatment and secondary prevention in stroke because the pathophysiology of stroke involves atherosclerotic plaque disruption and subsequent thrombosis. Aspirin exerts its antiplatelet action by irreversibly inhibiting the cyclooxygenase enzyme, blocking the prostaglandin mediated pathway of platelet activation. Ticlopidine and clopidogrel,both thienopyridines which are structurally related and act by selectively inhibiting adenosine diphosphate–induced platelet aggregation. Dipyridamole has both potent vasodilator and antiplatelet activity and act by by inhibiting phosphodiesterases or blocking uptake of adenosine.Epoprostenol ,another potent vasodilator is given to prevent platelet loss during renal dialysis.Glycoprotein (GP) IIb-IIIa antagonists, which involve a complex platelet glycoprotein IIb- IIIa complex, and mediate platelet aggregation via the binding of adhesive proteins such as fibrinogen and von Willebrand factor (vWF).Abciximab is a human-murine chimeric monoclonal antibody Fab fragment, which binds to the complex GP IIb-IIIa with high affinity.Eptifibatide,Tirofiban and lamifiban are competetive inhibitors of the GP IIb IIIa complex.**(Bennett and Brown, 2003).**

For preventing recurrent vascular events in patients with a history of stroke or TIA, antiplatelet therapy has been proven to be the best strategy available. The advantages of secondary stroke prevention associated with aspirin, other antiplatelet agents such as clopidogrel and combinations of antiplatelet drugs like aspirin and extended-release dipyridamole in preliminary therapy has been recognized by the current clinical practice guidelines by American Heart Association (AHA), American Stroke Association (ASA), American College of Chest Physicians (ACCP), American Academy of Neurology (AAN),

European Stroke Organization (ESO) and European Society of Cardiology (ESC).There has been great developments for the past two decades in antithrombotic agents for secondary stroke prevention. **(Diener and Wong, 2008).**

A series of trials in stroke prevention with antiplatelets have been carried out in past few years.CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial has shown that clopidogrel can better reduce the rate of ischaemic events and vascular events than aspirin. **(Ringleb et al., 2004)**. Randomised controlled trials in patients with coronary manifestations of atherothrombosis(CURE, CREDO) findings showed the sustained benefit of clopidogrel over the standard treatment including aspirin. **(Mehta et al., 2001)**. The therapeutic benefits were all achieved along with an acceptable increase in the risk of major bleeding complications. Thus, these trials gave the motivation to undertake MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients), to find out whether aspirin added to clopidogrel would further reduce the risk of recurrent ischaemic vascular events in high-risk patients after transient ischaemic attack or ischaemic stroke. **(Diener et al., 2004).**

Patients who survive a stroke or TIA are especially vulnerable to recurrent cerebrovascular events and most likely to suffer other forms of cardiovascular disease, including coronary artery disease, congestive heart failure, atrial fibrillation and peripheral vascular disease. The long term stroke recurrence risk ranges from 4-12% annually with a particularly heightened risk in first 6 months after an event.These conditions predispose to a high term mortality after stroke. Studying the effectiveness of mono and dual antiplatelet therapy will help in improving drug use and thereby increasing the quality of life in stroke patients.

Review of Literature

REVIEW OF LITERATURE

The World Health Organization(WHO) clinically defines stroke as "the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin" **(World Health Organization.1989;Sudlow and Warlow.1996)**. This definition includes cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage, but excludes transient ischemic attack (TIA, which last for 24 hours), subdural or extradural hemorrhage and infarction or hemorrhage secondary to infection or malignancy **(Bonita, 1992).**

Hippocrates, the father of medicine, first recognized stroke 2400 years ago. At that time stroke was called as apoplexy, which means struck down by violence. However it was not until the mid 1600s that Jacob Wepfer found that some of the patients who died with apoplexy had bleeding in the brain, while arteries were blocked in some cases. Medical science continued to study the cases, symptoms and treatment of apoplexy and finally in 1928,apoplexy was divided into categories based on the blood vessels involved. Methods like contrast angiography and indicator dilution technique used to measure cerebral flow and metabolism were developed and first carotid endarterectomy was performed in 1950's.In the twentieth century, preventive measures like management of hypertension, use of anticoagulant aspirin gained importance. Diagnostic tools like Doppler ultrasonography, CT scan, Positron Emission Tomography (PET) scan were performed and implemented. In the 1980's while the incidence of stroke increased due to drug abuse, there was increased emphasis on identifying the risk factors for stroke, especially in women and minorities. Cigarette smoking was established as a major risk factor and the cessation of which produced a significant risk reduction by two years **(National Survey on Drug Use and Health, 2005 and 2006)**. That decade also saw improved outcome with early aneurysm surgery, treatment

and isolated systolic hypertension in the elderly and use of newer drugs and newer diagnostic tools like MRI helped to treat and reduce the incidence of stroke. Secondary prevention trials emphasized importance of reducing blood pressure and cholesterol. The FDA approved t-PA,a drug that dissolves clot blocked brain arteries, to treat stroke in the first three hours. The addition of dypyridamole, a vasodilator to low dose aspirin was found to increase secondary stroke prevention. It was in 1990's that a wealth of information was obtained on the prevention and management of stroke through various researches **(Stroke Center, 2006)**.

Epidemiology of stroke:

Approximately, 20 million people suffer from stroke each year and out of these 5 million will not survive.85% of global deaths from stroke occurs in developing countries. It also causes functional impairments, 20% survivors require institutional care after 3 months and disability occurs in 15-30%.Stroke is a life-changing event which not only affects the person but also his family and caregivers **(Balucani, et al., 2010).**

Epidemiological status in Asian countries:

Stroke is the major cause of mortality and morbidity in Asian countries **(Pandian, et al., 2007)**. In Asian people, intracranial arterial atherosclerotic disease is the more common than extra cranial disease **(Jiang, et al., 2006)**. Many studies have shown that there are significant racial-ethnic differences in the topographical distribution of atherosclerotic lesions.Chinese **(Sacco, et al., 1992)** Japanese **(Mitsuyama, et al., 1979)**, Hispanics and Blacks **(Sacco, et al., 1995)**, have a greater preponderance of intracranial atherosclerosis than whites **(Kaul, et al., 2002)**.Within Asians, the reported rates of intracranial stenosis vary. Chinese populations showed higher rates than Japanese or Korean populations **(Suh, et al., 2003)**. A recent study comparing stroke disorders among three Asian races in Singapore

revealed that Chinese had higher prevalence of stroke when compared to Indians and Malay Singaporeans **(Venkatasubramanian,et al., 2005)**.

Epidemiological status in India :

Current demographic trends suggest that the population of India will survive through the peak years of occurrence of stroke (age 55-65 years),and stroke survivors in elderly with varying degree of residual disability will become a major health burden.In India,a multicentric,prospective,hospital based case control study in the west central region revealed that diabetes mellitus,hypertension,tobacco use and low hemoglobin rather than cholesterol level were the most important risk factors for stroke (**Dalal.P.M, 1997**). In India, the burden of stroke is growing with increasing urbanization pattern **(Thammaraj, et al., 2005)**. The estimated deaths due to stroke account for 1.2 % of all the deaths in India **(Anand,et al., 2001)**. A first community based study on stroke was carried out in and around the town of Vellore in South India **(Abraham, et al., 1970)** during the period of 1969-1971,followed by the study in Rohtak in North India during 1971-1974 **(Bansal, et al., 1973)**. A cross sectional community based case control study for risk factor analysis on stroke disorders was conducted for the first time in the city of Kolkata, demonstrated that hypertension was the most important risk factor for stroke **(Banerjee, et al., 2001)**.

Classification of stroke:

Stroke is a clinical syndrome which can be subdivided into two broad categories according to its pathophysiology:

1) Ischemic strokes are caused by either cerebral thrombosis or embolism, accounting for 50-85% of all strokes worldwide.

2) Hemorrhagic strokes caused by subarachnoid hemorrhage or intracerebral hemorrhage, which account for 1%-7% and 7%-27% respectively of all strokes worldwide.

I. Ischemic Stroke

Atherosclerotic cerebrovascular disease (20%)

- Hypoperfusion
- Arteriogenic emboli

Penetrating artery disease ("Lacunes")(25%)

Cardiogenic embolism

- Atrial fibrillation
- Valve disease
- Ventricular thrombi
- Other
- Cryptogenic stroke (30%)

Other, unusual causes (5%)

- Prothrombic states
- Dissections
- Arteritis
- Migraine/Vasospasm
- Drug abuse

II. Primary Hemorrhage

- Intraparenchymal
- Subarachnoid **(Gregory, et al.2002)**.

Up to 90% of all strokes are found to be ischemic in nature, while 10% resulting from intracerebral hemorrhage or subarachnoid hemorrhage . The majority of ischemic strokes are found to be of arterial origin such as atherothrombosis— which is a generalized, diffuse and progressive polyvascular disease. In most of acute ischemic strokes, unstable angina, acute MI, sudden cardiac death, and peripheral arterial disease (PAD), atherothrombosis have a key role **(Balucani, et al., 2010)**.

PATHOPHYSIOLOGY

Stroke is defined as an "acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain" **(Goldstein, et al., 1989)**. The two main types of stroke are ischemic and hemorrhagic, accounting for approximately 85% and 15%, respectively **(Hickey, 2003)**.When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of the glucose and oxygen they need to function. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. Approximately 45% of ischemic strokes are caused by small or large artery thrombus,20% are embolic in origin, and others have an unknown cause **(Hickey, 2003)**. Thrombosis can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the injured vessel. The endothelial injury (roughing) permits platelets to adhere and aggregate, then coagulation is activated and thrombus develops at site of plaque. Blood flow through the extracranial and intracranial systems

decreases, and the collateral circulation maintains function. When the compensatory mechanism of collateral circulation fails, perfusion is compromised, leading to decreased perfusion and cell death. During an embolic stroke, a clot travels from a distant source and lodges in cerebral vessels. Microemboli can break away from a sclerosed plaque in the carotid artery or from cardiac sources such as atrial fibrillation, patent foramen ovale, or a hypokinetic left ventricle **(Hickey, 2003)**. Emboli in the form of blood, fat, or air can occur during surgical procedures, most commonly during cardiac surgery, but also after long bone surgeries **(Warlow et al., 2001)**.Less common causes of ischemic stroke include carotid dissection **(Bader & Littlejohns, 2004)** and the presence of coagulopathies, such as those resulting from antiphospholipid antibodies **(APASS Investigators, 2004)**. Other causes include arteritis, infection, and drug abuse, such as the use of cocaine **(Blank-Reid, 1996; Hickey, 2003)**. While still not completely understood, the presence of periodontal disease and tooth loss is also an associated risk for ischemic stroke **(Joshipura, Hung, Rimm, Willett, & Ascherio, 2003)**. As a thrombosis or emboli cause a decrease in blood supply to the brain tissue, events occur at the cellular level, referred to as the ischemic cascade. Neurons and support cells require a careful balance of variables such as temperature, pH, nutrition, and waste removal in their environment to function optimally **(Hinkle & Bowman, 2003)**. Intensive basic scientific research during the last two decades has given healthcare professionals an increased understanding of the ischemic cascade in the format of the precise environmental alterations involved in the pathophysiology of ischemic injury at the cellular level. Understanding the ischemic cascade has led to the concept of a therapeutic time window for treatment possibilities. Often, there is a core region of dead cells surrounded by an area of hypoperfused tissue. The hypoperfused area may be rescued; this area is referred to as the penumbra region **(Muir et al., 2006)**. Neuroprotection is a broad term that refers to pharmacological and nonpharmacological treatments used to halt the cellular events in the

ischemic cascade, forming the theoretical basis for many of the acute stroke therapies under study **(Lees, et al., 2006**) as well as the rationale for intervening within a therapeutic time window following ischemic stroke.

TREATMENT FOR ISCHEMIC STROKE

Initial management

The initial management of acute ischemic stroke involves medical stabilization, including airway protection and ventilatory and hemodynamic support, followed by neurologic assessment, brain imaging, and evaluation of the appropriateness of thrombolytic therapy.

Airway and ventilatory support:

Patients with acute stroke are at risk for respiratory failure from aspiration and pneumonia, often in the setting of difficulty in protecting the airway and clearing secretions because of facial or bulbar weakness or an altered level of consciousness. Hypoxemia may worsen the injurious effects of cerebral ischemia, and patients must be monitored closely with a goal to keep oxygen saturation greater than 95%. If a patient requires endotracheal intubation, short-acting sedatives should be used, and the hemodynamic changes associated with intubation should be minimized. No prospective trials have been undertaken to establish the ideal mode of ventilation in intubated stroke patients. A commonly used mode for patients who are awake but in need of airway protection is pressure support ventilation, whereas synchronized intermittent mandatory ventilation or assist control ventilation is recommended for patients who have intracranial hypertension or are comatose. Excessive positive end-expiratory pressures may be deleterious in patients with elevated intracranial pressure (ICP) .Mechanically ventilated patients frequently require sedation; however, sedatives may cause hypotension and additional brain injury by lowering cerebral perfusion

pressure . Propofol, popular because of its short duration of action, has been associated with a ‘‘propofol infusion syndrome’’ when used at high doses for prolonged periods **(Vasile, et al., 2003)**. This syndrome originally was described in pediatric patients, but it also can occur in adults. It presents with metabolic acidosis, rhabdomyolysis, hypotension, bradyarrhythmias,and death . Frequent discontinuation of sedatives is indicated to monitor carefully for changes in the patient’s neurologic status.

Blood pressure and fluid management:

Patients with acute ischemic stroke often have elevated blood pressures in the first few days after symptom onset. Elevated blood pressure may occur for a variety of reasons, including physiologic compensation for cerebral ischemia, increased ICP, pain, or long-standing underlying hypertension . Advantages of treating hypertension in acute ischemic stroke include concerns for hemorrhagic transformation of the ischemic infarct and worsening cerebral edema. Lowering blood pressure may compromise cerebral blood flow in the area surrounding the infarct, resulting in stroke extension. In normotensive individuals, cerebral blood flow is maintained over a wide range of mean arterial pressures (50–150 mm Hg) . Chronically hypertensive patients require a higher range of mean arterial pressures to maintain normal cerebral blood flow . Because many stroke patients have long-standing hypertension, blood pressure lowering may result in cerebral hypoperfusion and worsening of ischemia. It is generally accepted that elevated blood pressures should not be lowered, unless the patient has received thrombolytic treatment; has a hypertensive emergency (aortic dissection, hypertensive encephalopathy, acute renal failure, acute pulmonary edema, or acute myocardial infarction); or has another contraindication to elevated blood pressure, such as recent surgery. In the absence of controlled clinical trials, the American Stroke Association guidelines recommend that antihypertensive agents should be withheld unless the systolic blood pressure is greater than 220 mm Hg or the diastolic blood pressure is greater than 120

mm Hg . If patients have received thrombolytic therapy, the guidelines advocate maintaining systolic blood pressure less than or equal to 180 mm Hg and diastolic blood pressure less than or equal to 105 mm Hg. If blood pressure lowering is indicated, it should be instituted cautiously to avoid hypotension. A variety of intravenous agents maybe used to lower blood pressures.Adrenergic blocking agents (labetalol), calcium channel blockers (nicardipine), and angiotensin-converting enzyme inhibitors (enalaprilat) are preferred in patients with acute stroke because these agents are less likely to cause cerebral vasodilation and ICP elevation, effects that might be anticipated with sodium nitroprusside or hydralazine .Some patients with acute cerebral ischemia resulting from severe extracranial or intracranial vessel stenosis may benefit from induced hypertension . Typically, mean arterial pressure is increased 20% to 25% from baseline using intravenous isotonic fluids, phenylephrine, dopamine, or norepinephrine, while the patient's neurologic status and hemodynamic stability are monitored closely. The impact of this therapy on stroke outcome is being evaluated in ongoing clinical trials. In patients with ischemic brain injury, a key therapeutic goal is to maximize brain perfusion and collateral blood flow to the injured area. It is important to assess the patient's volume status and correct any dehydration.Stroke patients may be dehydrated on admission, and many of them cannot tolerate intake of oral fluids, normal saline infusions are therefore started immediately. Hypotonic fluids should be avoided because these may contribute to worsening of cerebral edema and increased ICP .

Neurologic examination:

Assessing the patient for neurologic deficits may be accomplished in an efficient and reproducible manner by using the National Institutes of Health Stroke Scale (NIHSS). This is a series of neurologic tests designed to assess the patient's level of alertness; comprehension; and motor, sensory, visual, and language function **(Caulfield and Wijman, 2008).**

Treatment of acute ischemic stroke

1. Thrombolytic therapy

Thrombolytic therapy for acute ischemic stroke was first proposed in the 1950's;however intracranial hemorrhage was such a ,limiting factor that use of thrombolytic as a therapy became dormant until just recently, when better understanding about brain hemorrhage, use of plasminogen activators, and better imaging techniques have shed new light on this type of therapy in acute ischemic stroke **(Dumo, et al., 1997)**.The therapeutic effect of tissue plasminogen activators are to activate plasmin and thereby lyse fresh thromboemboli.Agents include streptokinase,anisolysed plasminogen streptokinase activator complex (APSAC),and tissue plasminogen activator (t-PA) single chain (alteplase) **(Bradberry and Fagan, 2002)**.

2. Anticoagulants

Anticoagulants reduce the formation of fibrin clots. Three major types of anticoagulants are available: heparin and related products, which must be used parentrally;direct thrombin inhibitors,which also must be used parentrally;and the orally active coumarin derivatives(eg.warfarin) have been developed. Direct thrombin inhibitors include Lepirudin is a recombinant form of the leech protein hirudin and Bivalirudin is a modified form of hirudin.

3. Antiplatelet agents:

Antiplatelet drugs (aspirin, dipyridamole, clopidogrel, ticlopidine, *prasugrel* abciximab, eptifibatide, and tirofiban) act on specific targets to inhibit platelet activation and aggregation .Clopidogrel effectively inhibits Adenosinediphosphate induced platelet activation and aggregation by selectively and irreversibly blocking the P2Y12 receptor on the platelet membrane. Aspirin acts by irreversibly acetylating the cyclooxygenase (COX-1)

enzyme, thus suppressing the production of thromboxane A2 (TXA2) and inhibiting platelet activation and aggregation.. **(Balucani, et al., 2010)**

4. Mannitol

Mannitol,an osmotic diuretic may be administered intravenously to reduce intracranial pressure.

5. Surgical therapy:

Generally the goal of surgical procedure is to remove the source of occlusion and /or embolus and hopefully to increase cerebral blood flow to the ischemic area.

Carotid endartectomy (CEA) is the most common surgical procedure used for occlusive cerebrovascular disease. This procedure has been popular since its introduction over 30 years ago.

REHABILITATION

Rehabilitation helps the person gain back lost abilities to become more independent. It usually begins while the patient is still in acute care. For many patients, it continues afterward, either as a formal rehabilitation program or as individual rehabilitation services. Many decisions about rehabilitation are made by the patient, family, and hospital staff before discharge from acute care.Rehabilitation includes physiotherapy,speech therapy and occupational therapy.

The goal in rehabilitation is to improve function so that the stroke survivor can become as independent as possible. This must be accomplished in a way that preserves dignity and motivates the survivor to relearn basic skills that the stroke may have taken away - skills like eating, dressing and walking (National Stroke Association, 2012).

Risk Factors for Ischemic Stroke

Nonmodifiable Risk Factors or Risk Markers:

Age, gender, race, ethnicity, and heredity have been identified as markers of risk for stroke. Although these factors cannot be modified, their presence helps identify those at greatest risk, enabling vigorous treatment of those risk factors that can be modified. Age is the single most important risk factor for stroke. For each successive 10 years after age 55, the stroke rate more than doubles in both men and women. Stroke incidence rates are 1.25 times greater in men, but because women tend to live longer than men, more women than men die of stroke each year.

Potentially Modifiable Risk Factors for Ischemic Stroke

Hypertension

Hypertension is the single most important modifiable risk factor for ischemic stroke. Most estimates for hypertension indicate a relative risk of stroke of approximately 4 when hypertension is defined as systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg. A summary of seven studies assigning a relative risk of 1 for borderline or mild hypertension determined the relative risk to be about 0.5 at a blood pressure of 136/84 mm Hg and about 0.35 at a blood pressure of 123/76 mm Hg **(MacMahon and Rodgers, 1994)**. From the lowest to the highest level of blood pressure in this summary, risk is increased about 10-fold. Although clearly important even in the elderly, the impact of hypertension may decrease with age: the odds ratio is 4 at age 50, decreasing to 1 by age 90. From population surveys the prevalence of hypertension is about 20% at age 50, about 30% at age 60, 40% at age 70, 55% at age 80, and 60% at age 90 .When the Joint National Committee V definition is used (≥140/90 mm Hg or on antihypertensive medication), prevalence increases to about 45% at age 50, >60% at age 60, and >70% at age 70. **(National**

Center for Health Statistics, 1986). The prevalence of hypertension is greater in blacks than in whites. The efficacy of antihypertensive treatment has been well established in clinical trials. In a summary of 17 treatment trials of hypertension throughout the world involving nearly 50000 patients, there was a 38% reduction in all strokes and a 40% reduction in fatal stroke favoring systematic treatment of hypertension. This effect was true in whites and blacks and at all ages. Treatment was also highly effective in preventing stroke in elderly persons with isolated systolic hypertension, the most prevalent form of hypertension in persons older than 65. Importantly, there was no less impact on stroke prevention above age 80, with incidence reduced by 40% **(SHEP Cooperative Research Group, 1991).**

Cardiac disease

Various cardiac diseases have been shown to increase the risk of stroke. Atrial fibrillation (AF) is the most powerful and treatable cardiac precursor of stroke. The incidence and prevalence of AF increases with age. With each successive decade of life above age 55, incidence of AF doubles **(Benjamin, et al., 1994)**. Using data from four population-based studies and the US census, it has been estimated that 2.2 million Americans have intermittent or sustained AF. Prevalence above age 65 is estimated to be 5.9%. Data from the Framingham Study and hospital discharges suggest that the prevalence of AF in the US population is increasing. The aging of the population, the increasing incidence of AF with age, and the increasing prevalence of AF suggest that AF will result in increasing rates of morbidity and mortality in the population.

Diabetes and Glucose Metabolism

Persons with diabetes have an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal

blood lipids. Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes with a relative risk of ischemic stroke in persons with diabetes from 1.8 to 3.0. Among Hawaiian Japanese men in the Honolulu Heart Program, those with diabetes had twice the risk of thromboembolic stroke of persons without diabetes that was independent of other risk factors **(Burchfiel, et al., 1994)**. In a population-based cohort, persons with diabetes had a risk-factor adjusted relative risk of stroke of 1.8 in men and 2.2 in women. In the Framingham study, persons with glucose intolerance had double the risk of brain infarction than that of nondiabetic persons.

In addition to the role of glucose status (normal, impaired glucose tolerance, or diabetic), there are other aspects of glucose metabolism that may play a role as a risk factor for ischemic stroke—specifically hyperinsulinemia and increased insulin resistance (the relative inability of insulin to enhance glucose disposal). Both were shown to be risk factors for ischemic stroke among subjects with normal glucose status **(Shinozaki, et al., 1996)**. In non-Hispanic white and Hispanic subjects, increased insulin resistance is associated with increased atherosclerosis of the carotid arteries independent of glucose status, insulin levels, and other major cardiovascular risk factors **(Howard, et al., 1996).**

Lipids

While hypercholesterolemia is an important modifiable risk factor for coronary heart disease, the link to ischemic stroke remains uncertain. However, data clearly support the positive relation between total and LDL cholesterol and a protective influence of HDL cholesterol on extracranial carotid atherosclerosis **(Heiss, et al., 1991)**. In secondary analyses, the Scandinavian Simvastatin Survival Study (4S) found a reduction of fatal or nonfatal stroke with simvastatin versus placebo (RR=.70, 95% confidence interval .52, .96), and the Asymptomatic Carotid Artery Plaque Study (ACAPS) reported fewer strokes in the lovastatin

versus placebo group (5 versus 0**) (Simvastatin Survival Study, 1994)**. A pooled analysis of four pravastatin trials disclosed a 46% reduction in risk of stroke (*P*=.054**) (Byington, et al., 1995).**

Cigarette Smoking

Cigarette smoking increases risk (RR) of ischemic stroke nearly two times **(Shinton, and Beevers, 1989)**, with a clear dose-response relation. In both the Framingham Study and the Nurses' Health Study **(Kawachi, et al., 1993)** cessation of smoking led to a prompt reduction in stroke risk—Major risk was reduced within 2 to 4 years. This reduction in risk occurred throughout the age spans of these studies and in heavy as well as moderate smokers.

Alcohol

Moderate consumption of alcohol may reduce cardiovascular disease, including stroke. Recent epidemiological studies have shown a U-shaped curve for alcohol consumption and coronary heart disease mortality, with low to moderate alcohol consumption associated with lower overall mortality. In an overview analysis of stroke studies, a J-shaped association curve was suggested for the relation of moderate customary alcohol consumption and ischemic stroke**. (Camargo, 1989).** This was most consistent for white populations; however, little if any association existed for Japanese and possibly black populations. Increasing alcohol consumption increases risk for brain hemorrhage. **(Gorelick, 1995).**

Illicit Drug Use

Drug abuse is a major social problem, with cocaine the substance most commonly associated with stroke **(Kelly, et al., 1992).** Other drugs linked to stroke include heroin, amphetamines, LSD, PCP, "T's and Blues," and marijuana. Case reports have also linked over-the-counter sympathomimetic decongestants, cold remedies, and diet aids (eg,

phenylpropanolamine), ephedrine, and pseudoephedrine with hemorrhagic and, less often, ischemic stroke. The bulk of information about stroke and drug use and abuse is derived from case reports or case series, with many reports confounded by multiple drugs used. There are sparse epidemiological data relating drug use to stroke.

Lifestyle Factors (Obesity, Physical Activity, Diet, and Acute Triggers)

Various lifestyle factors have been associated with increased stroke risk. These include obesity, physical inactivity, diet, and acute triggers such as emotional stress. Obesity has been associated with higher levels of blood pressure, blood glucose, and atherogenic serum lipids, which are independent risk factors for stroke. In the Framingham study, obesity defined as a Metropolitan Life chart relative weight greater than 30% above average was a significant independent contributor to incidence of brain infarction in men aged 35 to 64 and women aged 65 to 94. In the Honolulu Heart Study, obesity was identified as an independent factor related to stroke incidence. The pattern of obesity may be important; central obesity manifested by abdominal deposition of fat, rather than obesity involving the hips and thighs, has been related to the occurrence of atherosclerotic disease **(Abbott, et al., 1994).**

Oral Contraceptives

Oral contraceptives with an estrogen content >50 µg, the preparations used in the 1960s and 1970s, were strongly associated with the risk for stroke. Recently a study of low-dose oral contraceptives (<50 µg estrogen) disclosed no increased risk of stroke in more than 3.6 million woman-years under observation **(Petitti, et al., 1996).**

Migraine

While migraine has been identified as an independent risk factor for ischemic stroke in men older than 40 in the Physicians' Health Study, no association was found in other studies after adjusting for other stroke risk factors **(Buring, et al., 1995).** Although there may

be an association between migraine and stroke, this association must be put in the context of the absolute risk of stroke. It has been estimated that the presence of migraine increased the incidence of stroke in young women from 10 in 100 000 woman-years to 19 in 100 000 woman-years. Therefore, the absolute risk of stroke associated with migraine is very small.

Transient Ischemic Attacks

The average risk of stroke in patients with TIAs is about 4%. After adjustment for major cardiovascular risk factors predisposing a patient to stroke, a TIA remains a significant independent risk factor for both stroke and myocardial infarction. TIA referable to a high-grade carotid artery stenosis carries a higher risk for stroke than those beyond a mild stenosis, and the risk with hemispheric ischemic symptoms is greater than for retinal ischemia. Recent-onset TIA has a higher risk for ischemic stroke than remote TIA, and the same may be true for "crescendo" TIA. Various other clinical features have a major effect on the absolute risk for individual patients . It is clear that antiplatelet therapy substantially reduces risk for stroke (and other atherothrombotic events such as myocardial infarction and vascular death) in all high-risk patients, including those with TIAs. **(Sacco, et al.,1997)**

DRUGS AND MECHANISM OF ACTION

Revelation of the multiple mechanisms which are involved in platelet thrombus formation provides opportunities for selectively inhibiting the pathways most significant to the pathophysiology of atherothrombosis . Along with other secondary prevention measures, antiplatelet therapy remains a key component of atherothrombotic event prevention. Numerous trials and meta-analyses have confirmed the effect of an antiplatelet therapy to reduce the risk of vascular event recurrence in patients with previous stroke or TIA. However, controversies exist and the debate is now being focused on the optimal antiplatelet regimen. The majority of research in secondary stroke prevention supports the clinical value

of aspirin. Whether aspirin remains the best available antiplatelet drug for stroke prevention and if it should be used alone or in combination with another antiplatelet agent more effective than aspirin monotherapy are still a matter of debate **(Balucani, et al., 2010).**

Antithrombotic drugs act by blocking the platelet aggregation and activation at many points in the thrombotic cascade.They consist of aspirin, thienopyridines (clopidogrel and its predecessor ticlopidine), intravenous GP IIb/IIIa inhibitors, which block the final common pathway of platelet activation and aggregation, unfractionated heparin and low-molecularweight heparin, and direct thrombin inhibitors. Presently, available antiplatelet drugs (aspirin, dipyridamole, clopidogrel, ticlopidine, *prasugrel* abciximab, eptifibatide, and tirofiban) act on specific targets to inhibit platelet activation and aggregation .Clopidogrel effectively inhibits Adenosinediphosphate induced platelet activation and aggregation by selectively and irreversibly blocking the P2Y12 receptor on the platelet membrane. Aspirin acts by irreversibly acetylating the cyclooxygenase (COX-1) enzyme, thus suppressing the production of thromboxane A2 (TXA2) and inhibiting platelet activation and aggregation **(Balucani, et al., 2010).**

MONO AND DUAL ANTIPLATELET THERAPY

Kral, et al conducted a study on characteristics of particular antiplatelet agents as well as choice of antiplatelet treatment in various situations, based on the evidence and international recommendations. The study site was Stroke Center, Department of Neurology, Faculty of Medicine and Dentistry, Palacky University and University Hospital, Olomouc, Czech Republic and Department of Neurology, Central Military Hospital, Ruzomberok, Slovakia. The findings of the study were that Acetylsalicylic acid (ASA) is the only antiplatelet drug used in primary prevention, mainly to reduce the risk of myocardial infarction (MI), but also in women aged 45 years or more and in some patients with non-

valvular atrial fibrillation to reduce risk of IS/TIA.In the secondary prevention of noncardioembolic Ischemic stroke/Transient Ischemic Attack, ASA in combination with long release dipyridamole (DIP) and clopidogrel (CLOP) alone are considered first choice therapies. The choice of the particular antiplatelet agent should be individualized according to the patient risk factor profiles and treatment tolerance. ASA alone or triflusal can be used alternatively in patients who cannot be treated with either ASA+DIP or CLOP. The use of indobufen should be considered only in patients in need of temporary interruption of the antiplatelet therapy. Ticlopidine (TIC) should not be newly introduced into the treatment. Currently, insufficient data are available on the use of cilostazol in IS/TIA prevention.

The results of recent clinical trials on the use of antiplatelet therapy suggest that patients with a history of stroke or TIA may constitute a population distinct from patients with coronary or peripheral vascular disease. This may be caused, in part, by the differing etiologies of stroke and the increased vulnerability of cerebral vessels to bleeding. Indeed, dual antiplatelet therapy, which has been found to be beneficial for the treatment of acute coronary syndromes and percutaneous coronary interventions, does not confer secondary stroke protection. The emerging paradigm is that some level of platelet inhibition is required for secondary stroke protection; a level beyond which increased risk of bleeding arises. **James K. Liao, MD, 2007** suggested that since the vast majority of patients with ischemic stroke have recurrent stroke or transient ischemic attack, rather than myocardial infarction, as their next event, antiplatelet therapies for these patients should be administered according to what has been shown to be efficacious for secondary stroke protection rather than for myocardial protection. Combination therapies, which provide optimal platelet inhibition as well as vascular protection, may offer the best strategy for secondary stroke protection.

The fact that intensified antiplatelet therapy contributes to the reduction of major atherothrombotic complications in cardiovascular (CV) disease is widely accepted. In the setting of PCI (percutaneous coronary intervention) and acute coronary syndromes, dual antiplatelet therapy at optimal dosing and timing has significantly lowered the risk of thrombotic complications. There is a growing body of evidence that there is variability in response to antiplatelet treatments and this represents a potentially important clinical problem.

Understanding the mechanisms underlying this phenomenon is important in improving patient care, but due to the diversity of factors involved, a clear predictive model for responsiveness to antiplatelet therapy is still missing. Attempts have been made to characterize the efficacy of antiplatelet therapy using platelet function testing but based on current information, its routine use is not recommended particularly as costs and cost effectiveness have not been established and agreement between laboratory methods is lacking. Hence, it is necessary to identify risk factors for decreased efficacy of standard antiplatelet drug treatment. It may be useful to adjust antiplatelet therapy based on individual risk assessment, especially as new platelet inhibitors are being introduced or are in development including prasugrel as well as the non-thienopyridines, ticagrelor, elinogrel, the ATP analog cangrelor, and thrombin receptor antagonists. The article focuses on antiplatelet therapy in those patients who are at high risk for cardiovascular events and discusses the options for individual risk assessment and strategies to personalize therapy in the light of the large number of recent developments. **(Geisler, et al., 2010)**

A prospective study of consecutive patients with acute stroke who were admitted to 36 participating hospitals in China, India, Indonesia, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand, and Vietnam was conducted with the use of a simple identical

data sheet, the demographics and cardiovascular risk factors of each patient was recorded. Early death was defined as death on discharge from the acute hospital. 2403 patients were enrolled with ischemic stroke and 783 patients with intracerebral hemorrhage. Among patients with ischemic stroke, previous use of antiplatelet drugs and relatively young age group 56 to 75 years were protective factors; atrial fibrillation, ischemic heart disease, diabetes **(Jorgensen, et al., 1994)**, and ex-smoker status were risk factors for early death. Among patients with intracerebral hemorrhage, hypertension and young age group 56to 75 years old were associated with lower death rate, whereas diabetes was a risk factor for early death **(Haffner, et al., 1998)** .In Asian patients with stroke, previous use of antiplatelet drugs nearly halved the risk of early death in patients with ischemic stroke, whereas atrial fibrillation, ischemic heart disease, diabetes, and ex-smoker status were risk factors for early death **(Broderick, et al., 1992).** Among patients with intracerebral hemorrhage, diabetes was associated with early death, whereas young age group and hypertension were associated with lower death rates, though no clear explanation for the hypertension association could be discerned from the data available **(Wong, 1999).**

Clopidogrel along with aspirin for reduction of infarction in acute stroke or TIA with large artery stenosis and microembolic signals (CLAIR) trial was designed as a randomized, open-label and blinded-endpoint trial. Patients with acute ischemic stroke or TIA who had symptomatic large artery stenosis in the cerebral or carotid arteries and in whom microembolic signals were detected on transcranial doppler between,were arbitrarily assigned within 7 days of symptom onset to receive clopidogrel (300 mg for the first day, then 75 mg daily) plus aspirin (75–160 mg daily) or aspirin alone (75–160 mg daily) for 7 days . On days 2 and 7, microembolic signals on transcranial doppler monitoring was done.Proportion of patients with microembolic signals on day 2 were taken as primary endpoint .Out of 100

patients,93 had symptomatic intracranial stenosis in either the intracranial internal carotid artery or the middle cerebral artery: 45 of 46 in the dual therapy group and 48 of 52 in the monotherapy group. At day 2, 14 of 45 patients in the dual therapy group and 27 of 50 patients in the monotherapy group for whom data were available had at least one microembolic signal on transcranial doppler.Adverse events were found to be similar in both the groups. None of the patients had intracranial or severe systemic haemorrhage, except two patients in the dual therapy group who had minor haemorrhages. Combination therapy by means of clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis. Clinical trials are now essential to investigate whether this combination treatment also results in a reduction in stroke incidence **(Wong, et al., 2010).**

In 7599 high-risk patients with recent ischemic stroke or TIA and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day, a trial was carried out to compare aspirin (75 mg/day) with placebo.The trial was designed as a randomized, double-blind, placebo-controlled trial. Period of treatment and follow-up was 18 months.The primary endpoints included a composite of ischemic stroke, MI , vascular death, or rehospitalisation for acute ischemia (including rehospitalisation for transient ischemic attack, angina pectoris, or worsening of peripheral arterial disease).Analysis was by intention to treat which was done by means of log rank test and a Cox's proportional-hazards model. Compared with 636 (16·7%) in the clopidogrel alone group (relative risk reduction 6.4%, [95% CI –4·6 to 16·3]; absolute risk reduction was found to be 1% [–0·6 to 2·7] in the group receiving aspirin and clopidogrel, 596 (15.7%) patients reached the primary endpoint. Life-threatening bleedings were found to be higher in the group receiving aspirin and clopidogrel whereas clopidogrel alone accounted for (96 [2·6%] *vs* 49 [1·3%]; absolute risk increase 1·3% [95% CI 0·6 to 1·9]). Although major bleedings were found to be increased in the

group receiving aspirin and clopidogrel no variation was recorded in mortality.It was found that addition of aspirin to clopidogrel in high-risk patients with recent ischemic stroke or transient ischemic attack is linked with a non-significant difference in reducing major vascular events. On the other hand, the risk of life threatening bleeding was found to be increased by the addition of aspirin **(Diener, et al., 2004).**

Dual antiplatelet therapy is usually superior to mono therapy in preventing recurrent vascular events .A study was carried out to assess the safety and efficacy of triple antiplatelet therapy in comparison to dual therapy in reducing recurrent vascular events. Completed randomized controlled trials investigating the effect of triple versus dual antiplatelet therapy in patients with ischemic heart disease (IHD), cerebrovascular disease or peripheral vascular disease were identified using electronic bibliographic searches. Data were extracted on composite vascular events, myocardial infarction, stroke, death and bleeding and analyzed. Twenty-five completed randomized trials (17,383 patients with IHD) were involved which involved the use of intravenous GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), aspirin, clopidogrel and/or cilostazol. In comparison with aspirin-based therapy, triple therapy using an intravenous GP IIb/IIIa inhibitor, significantly reduced composite vascular events and myocardial infarction in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) and ST elevation myocardial infarction (STEMI). A significant reduction in death was also noted in STEMI patients treated with GP IIb/IIIa based triple therapy. Increased minor bleeding was noted in STEMI and elective percutaneous coronary intervention (PCI) patients treated with GP IIb/IIIa based triple therapy. Stroke events were too infrequent for us to be able to identify meaningful trends and no data were available for patients recruited into trials on the basis of stroke or peripheral vascular disease. Triple antiplatelet therapy based on intravascular GPIIb/IIIa inhibitors was more effective than aspirin-based dual therapy in reducing vascular events in patients with acute coronary

syndromes (STEMI and NSTEMI). Minor bleeding was increased among STEMI and elective PCI patients treated with a GP IIb/IIIa based triple therapy. In patients undergoing elective PCI, triple therapy had no beneficial effect and was associated with an 80% increase in transfusions and an eightfold increase in thrombocytopenia. Insufficient data exist for patients with prior ischemic stroke and peripheral vascular disease **(Geeganage, et al., 2010).**

Stroke is the most common neurological disease in China, and antiplatelet treatment is important for primary and secondary prevention.A study was conducted to describe the current status of antiplatelet treatment before, immediately after, and 1 month after ischemic stroke in the Qingdao area of China, and to determine the factors and potential barriers influencing use. A total of 1114 patients with acute ischemic stroke were enrolled from 11 hospitals in the Qingdao area.The frequency of antiplatelet treatment was 6.4% before the stroke, 91.5% in hospital, and 77.2% at 1 month. Aspirin pretreatment was independently associated with higher education level, higher income level, history of hyperlipidemia, and history of cerebral vascular disease. Antiplatelet treatment in hospital was independently associated with treatment in an urban hospital, National Institutes of Health Stroke Scale at onset, and statin use in hospital. Antiplatelet treatment at 1-month follow-up was independently associated with higher income level, diagnosis of transient ischemic attack, antiplatelet treatment in hospital, large artery atherosclerosis,and statin use at follow-up. Modified Rankin Scale ≥4 at 1-month follow-up and history of coronary heart disease were negatively associated with antiplatelet treatment at follow-up. This study documents the current status of antiplatelet treatment in primary and early secondary prevention of ischemic stroke in China **(Xin, et al., 2011).**

Aspirin, dipyridamole and clopidogrel are effective in secondary vascular prevention. Combination therapy with three antiplatelet agents might maximise the benefit of antiplatelet

treatment in the secondary prevention of ischemic stroke. A randomized, parallel group, observer-blinded phase II trial compared the combination of aspirin, clopidogrel and dipyridamole with aspirin alone. Adult patients with ischemic stroke or transient ischemic attack (TIA) within 5 years were included.One recurrent stroke occurred in a patient in the triple group who was noncompliant of all antiplatelet medications. The number of patients with adverse events and bleeding complications, and their severity, were significantly greater in the triple therapy group: Long term triple antiplatelet therapy was associated with a significant increase in adverse events and bleeding rates, and their severity, and a trend to increased discontinuations. However, the patients had a low risk of recurrence and future trials should focus on short term therapy in high risk patients characterized by a very recent event or failure of dual antiplatelet therapy **(Sprigg, et al., 2008).**

A systematic review was performed to define the relative and absolute risk of clinically relevant adverse events with the antiplatelet agents, aspirin and clopidogrel. Relative risks (RR) were determined by meta-analysis of 22 trials for aspirin versus placebo and from single studies for aspirin versus clopidogrel, aspirin versus aspirin/clopidogrel, and clopidogrel versus aspirin/clopidogrel.Aspirin increased the risk of major bleeding, major gastrointestinal (GI) bleeding, and intracranial bleeding versus placebo. No difference between 75-162.5 mg/day and _162.5-325 mg/day aspirin versus placebo was seen. The absolute annual increases attributable to aspirin were major bleeding: 0.13%; major GI bleeding: intracranial bleeding: 0.03% **(Derry and Loke, 2000).** No study compared clopidogrel with placebo. One study showed increased major GI bleeding (but not non-GI bleeding endpoints) with aspirin **(Yusuf, et al., 2001).** Low-dose aspirin increases the risk of major bleeding by _70%, but the absolute increase is modest: 769 patients need to be treated with aspirin to cause one additional major bleeding episode annually. Compared with clopidogrel, aspirin increases the risk of GI bleeding but not other bleeding; however, 883

patients would need to be treated with clopidogrel versus aspirin to prevent one major GI bleeding episode annually at a cost of over 1 million dollars **(McQuaid and Laine, 2006).**

Evidence for the effectiveness of dual antiplatelet therapy in stroke is inadequate. Patients with symptomatic carotid stenosis are at high danger of early recurrent stroke. In this group, asymptomatic microembolic signals (MES), detected by transcranial Doppler ultrasound (TCD), are considered to be the markers of future stroke and TIA.They suggest a substitute marker to assess antiplatelet therapy, however no multicenter study has evaluated the practicability of this approach. Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) is a randomized, double-blind study conducted in subjects with recently symptomatic _50% carotid stenosis **(De Bray and Glatt, 1995)**. Patients were first screened with TCD, and in case MES were detected, they were treated with clopidogrel and aspirin or aspirin monotherapy.TCD recordings were repeatedly made on days 2 and 7. Microembolic signals were detected in 110 of 230 patients out of them 107 were randomized.On day 7, 43.8% of dual-therapy patients were MES positive when compared with 72.7% in monotherapy patients. The secondary end point of MES frequency per hour was reduced when compared with baseline) by 61.4% in the dual-therapy group at day 7 and by 61.6% on day 2. There were 4 recurrent strokes and 7 TIAs in the monotherapy group in opposition to no stroke and 4 TIAs in the dual-therapy group .In patients with recent symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin was found to be more effective than aspirin alone in reducing asymptomatic embolization **(Markus, et al., 2005).**

Methodology

METHODOLOGY

Objective

The study was aimed to determine whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of secondary vascular events in patients after TIA or ischemic stroke.

Study design

It was a retrospective observational study with duration of six months.

Study setting

The study was conducted in the Department of Neurology, Kovai Medical Center and Hospital, a multi speciality hospital in Coimbatore, Tamil Nadu.

Study period

The study was conducted over a period of six months from June 2011 to December 2011.

Study population

Patients diagnosed with stroke attending the Neurology Clinic between January 2009 to January 2010, conforming to the study criteria.

Study criteria

Inclusion criteria

Patients of age > 40 years who are diagnosed with ischaemic stroke and treated with either mono (Clopidogrel) or dual (Clopidogrel +Aspirin) antiplatelet therapy.

Exclusion criteria

a) Patients who are less than 40 years of age.

b) Patients who are diagnosed with hemorrhagic stroke.

Sources of data

Data were collected from patients' case reports and treatment charts**.**

Study protocol

Ethical committee approval for conducting the study was obtained from Kovai Medical Center and Hospital. Records of patients on antiplatelet therapy from January 2009 to January 2010 were studied. Patients who met the study criteria were included in the study. Demographic characteristics of the patient including age, sex, occupation, smoking habits were collected. The other necessary findings like type of stroke, history of stroke, past medication history, type of antiplatelet therapy prescribed, number of recurrences were noted from patient's case reports and treatment charts. Data were entered in the data entry sheet. Analysis was based on the first recurrence of a cardiovascular event which was taken as the primary endpoint at any point during the follow-up period. The follow up period was taken as 18 months.

Statistical analysis

Demographic characteristics of the study population were expressed in percentage. Relative risks and associations were determined by using the 'chi-square test'. Values of $P \leq 0.05$ were considered to be significant.

Results

RESULTS

In this retrospective study, the effectiveness of mono and dual antiplatelet therapy in secondary prevention of vascular events was evaluated in a total of 38 patients with ischemic stroke. The identified patients were either on aspirin plus clopidogrel (dual) or only clopidogrel (mono) antiplatelet therapy.

Among the stroke patients, visiting the neurology clinic, 34.2 % of patients were found to have recurrence of vascular events after the study period. The mean age of the study population was found to be 61.36 years. In the population identified, the number of male patients were found to be 30 and female patients were 8 (Table 1, Figure 1).

The age of onset of the study population was found to be varying from 41 to 90 years. About 31% of the total study population, were in the age group of 61-70 years and they constituted the highest percentage of the total patients.29% were found to be in the 51-60 age group and 20% in the age group of 71-80 years.In the age group of 41-50,the percentage was 14% and 6% were noted in 81-90 age group. (Table 2,Figure 2). Mean age of patients taking dual therapy was found to be 61 and mean age in mono group was 64. In dual therapy group, 31% of patients had Ischemic stroke as qualifying event compared to 5 % in monotherapy.

In the male population, 86.6 % were prescribed dual therapy and 13.3 were prescribed with monotherapy (Table3,Figure3).In the female group, 87.5 % were prescribed dual therapy and 12.5 % were given monotherapy (Table 4,Figure 4).

In the total study population, 86.8 % were having hypertension as the risk factor.52.6 % patients were identified to be having diabetes and 28.9 % of patients had a previous history of stroke 60.5% had hypercholesterolemia and 10.5% were smokers (Table 5, Figure 5).

The mean age of the patients being prescribed dual therapy was found out to be 60.93 and mean age of the patients taking monotherapy was found to be 64.2 (Table 6).According to TOAST classification,2% were found to be having cardioembolism, 20% were having large artery atherothrombosis,12 % with small vessel occlusion in dual therapy group.20 % had cardioembolism and 60 % had small vessel occlusion in mono group (Figure 6).

Previous ischemic stroke, hypertension, diabetes, hypercholestrerolemia were found to be the most common risk factors in the population studied. Previous ischemic stroke were reported in 12 % of dual therapy group and 1% in mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was found to be a risk factor in 16% of dual therapy patients and 4% in monogroup. Hypercholesterolaemia was identified as risk factor in 19% of dual group and 4 % of mono group.11% of dual therapy patients and 2 % of mono therapy patients were smokers (Figure 7).

Out of the total study population, 36 patients had ischemic stroke as the qualifying event and 2 patients were having Transient Ischemic Attack. The event rate for ischemic stroke in dual therapy group was found to be 35.48 % and 0.2% for TIA. The event rate for TIA was found to be 0.5 % in dual group. The event rate was found to be 31.2 % in dual therapy group in patients whose age is greater than 61 and 41.1% in patients of age greater than or equal to 61 compared to the 33.3 % in mono group. The event rate in dual therapy group for males was found to be 42.3 % and 0.25 % in mono group. The event rate in dual therapy group for females was found to be 14.2 %.In patients having hypertension 0.4 % event rate was noted in dual therapy compared to 33.3 % in monotherapy. Diabetes patients had 0.25 % event rate in dual therapy and 0.25 % in monotherapy. Event rate in patients with previous ischemic stroke was found to be 1% in dual therapy and 1 % in monotherapy (Table 7).

The frequency of primary endpoint event was found out from the plot between the follow up period in months and number of patients at risk. The number of patients at risk of primary endpoints was found to be more increase in the follow up period in patients receiving dual therapy than those on mono therapy (Figure 8).

Univariate analysis of factors affecting primary endpoint showed that there was an association between recurrence of cardiovascular event and factors like gender, hypertension, previous ischemic stroke and antiplatelet therapy. Out of the total study population,8 patients having age less than 61 had recurrence with a p value < 0.20.In the age group ≥ 61, five patients were found to have recurrence.12 male patients and 1 female patient were found to have recurrence with a p value < 0.01.In patients with hypertension,13 cases of recurrences were found with a p value < 0.01.In patients with diabetes,5 cases were recorded with a p value < 0.7.In dual therapy group 12 cases of recurrences were noted compared to 1 case in mono therapy group with a p value <0.01 (Table 8).

The relative risk for recurrence were found out in the study population. In patients having ischemic stroke as qualifying event the relative risk of dual therapy was found to be 1.7742 times that of mono therapy. When TIA was the qualifying event, the relative risk was found to be the same for both mono and dual therapy. Relative risk with dual therapy was 0.9412 times than that of mono therapy in patients of age < 61 years and 1.2353 times in age ≥ 61 years. In male patients, relative risk with dual therapy was 1.6923 times than with mono therapy and in females it was found to be 0.7500 times that of monotherapy. Patients with hypertension had 0.9744 times the risk and those with previous ischemic stroke had 1.2821 times risk than with mono therapy. The relative risk in patients having diabetes was found to be equal in both dual and mono therapy (Table 9)

Tables and Graphs

TABLE 1: Gender wise distribution of total study population

Sl. No	Gender	Percentage of patients
1.	Male	79%
2.	Female	21%

FIGURE 1: Gender wise distribution of total study population

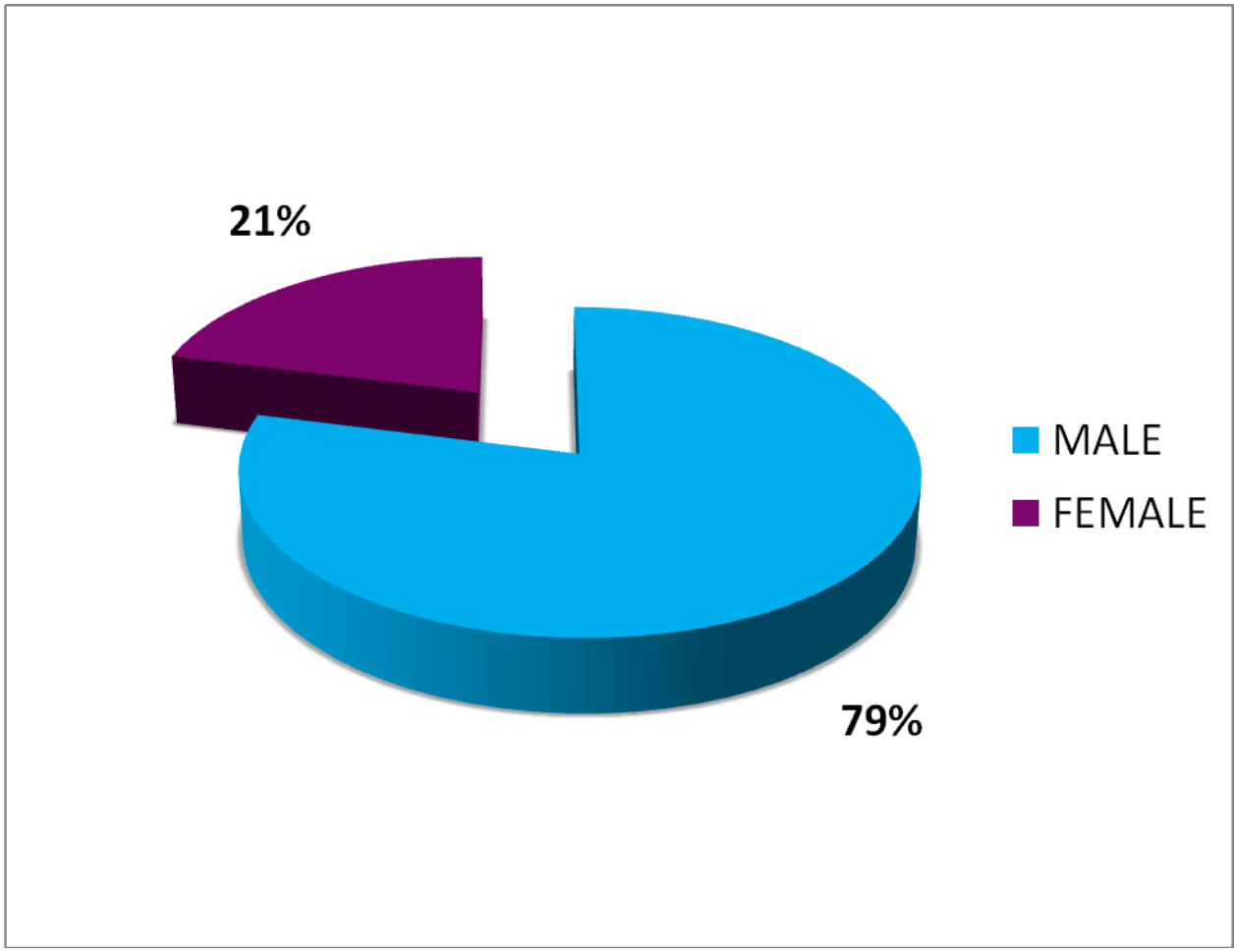


TABLE 2: Age wise distribution of the study population

Sl. No	Age group	Percentage of patients
1.	41-50	14
2.	51-60	29
3.	61-70	31
4.	71-80	20
5.	81-90	6

FIGURE 2: Age wise distribution of the study population

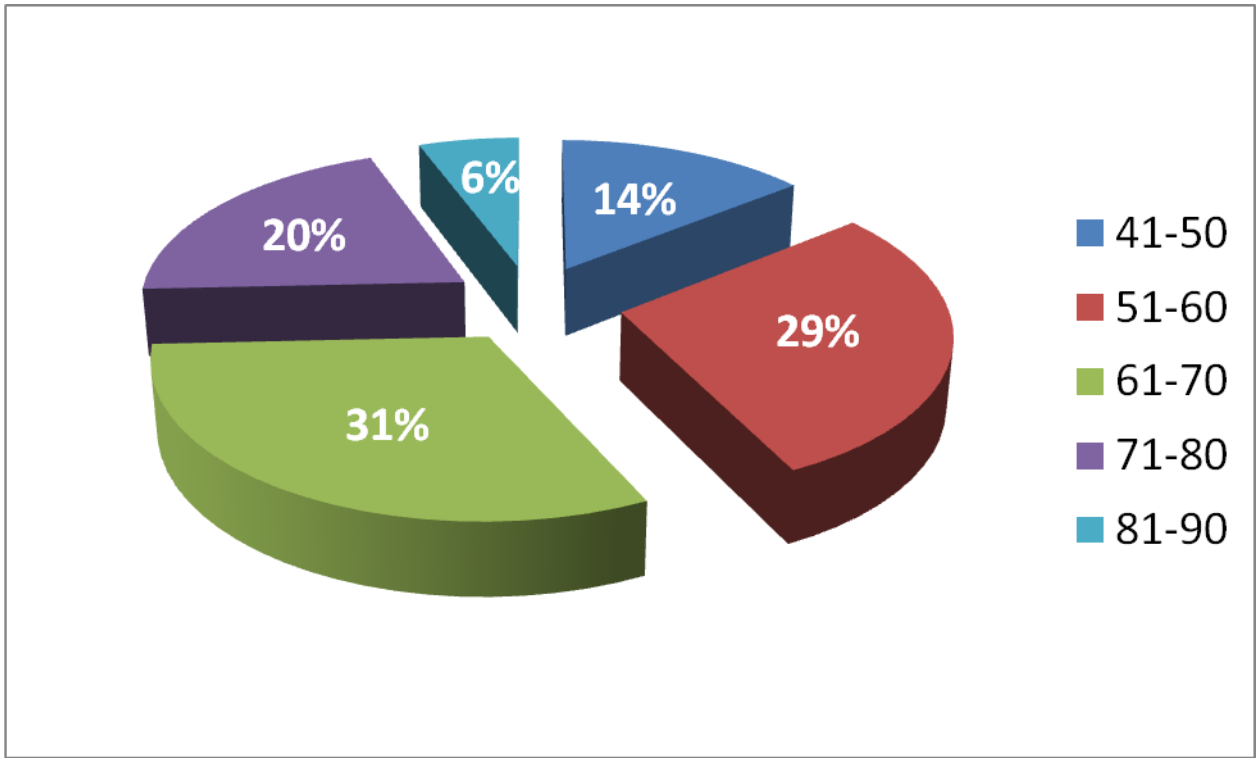


TABLE 3: Type of Antiplatelet therapy prescribed in male patients.

MALE

Sl.No	Antiplatelet therapy prescribed	Percentage of patients
1.	DUAL	86.6
2.	MONO	13.3

Dual : Aspirin + Clopidogrel

Mono: Clopidogrel

FIGURE3: Type of Antiplatelet therapy prescribed.

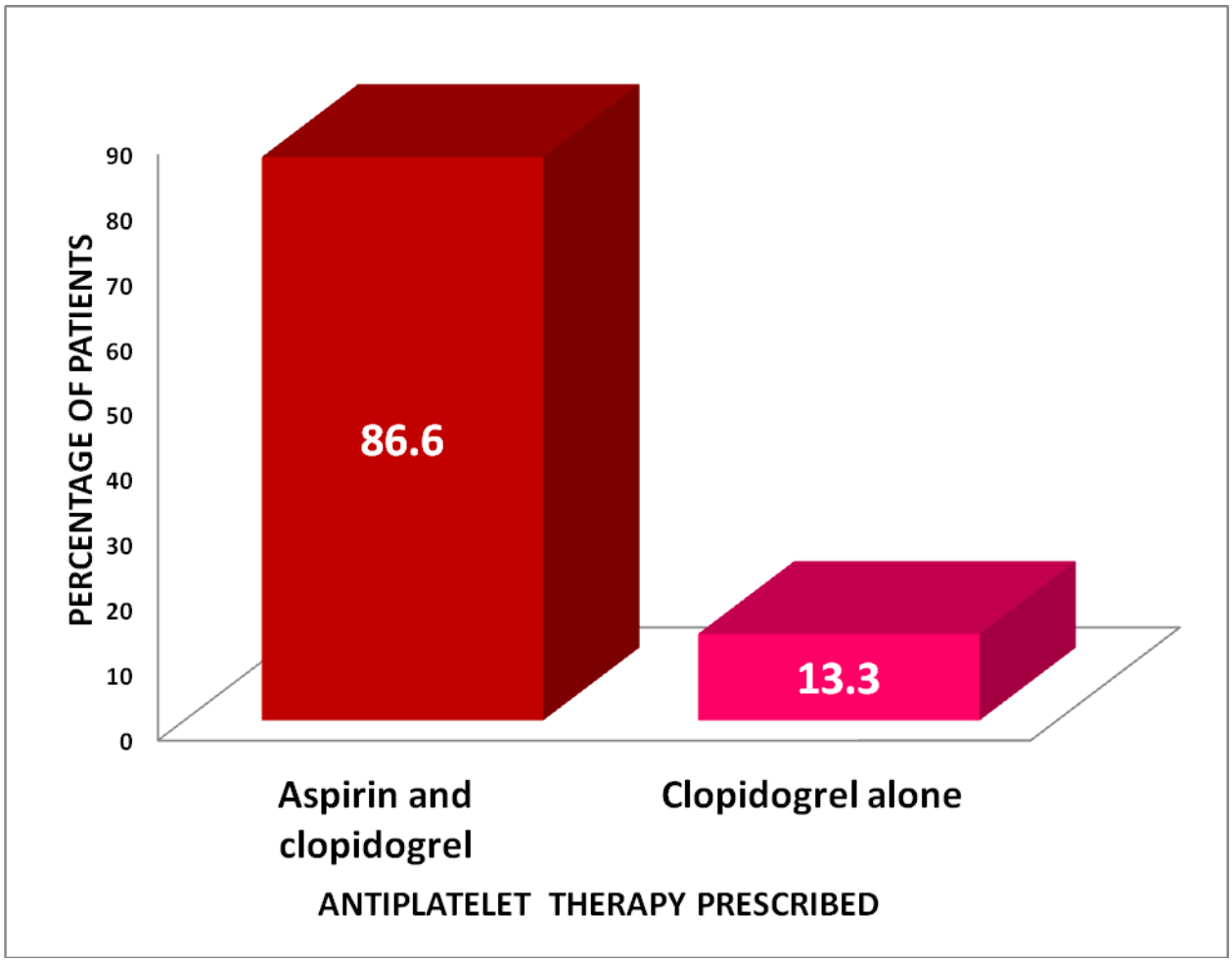


TABLE 4: Type of Antiplatelet therapy prescribed in female patients.

FEMALE

Sl.No	Antiplatelet therapy prescribed	Percentage of patients
1.	DUAL	87.5
2.	MONO	12.5

Dual : Aspirin + Clopidogrel

Mono: Clopidogrel

FIGURE4: Type of Antiplatelet prescribed.

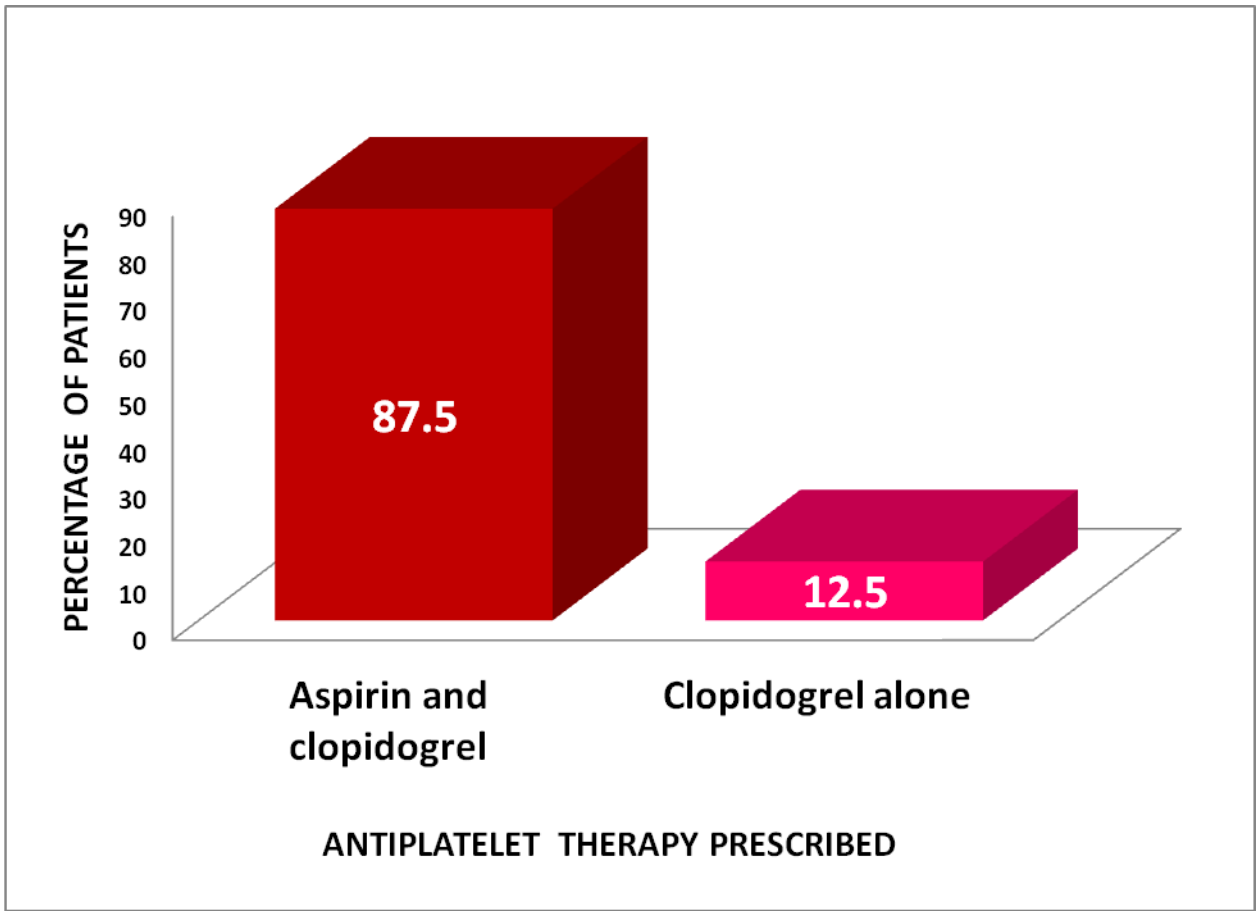


TABLE 5: Risk factors and medical history of the study population.

Sl.No	Risk factors	percentage of patients
1.	Hypertension	86.8
2.	Diabetes	52.6
3.	Previous ischemic stroke(before qualifying event)	28.9
4.	Hypercholesterolemia	60.5
5.	Smoking	10.5

FIGURE 5: Risk factors and medical history of the study population.

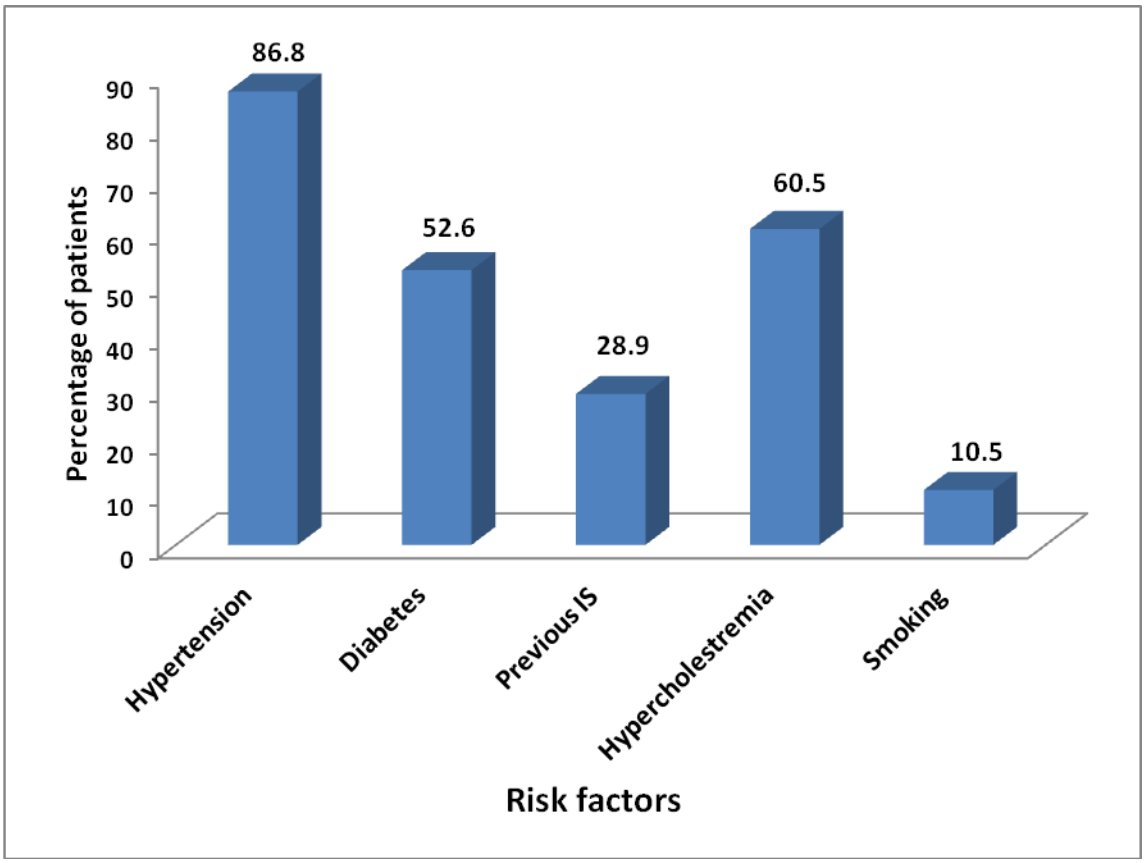
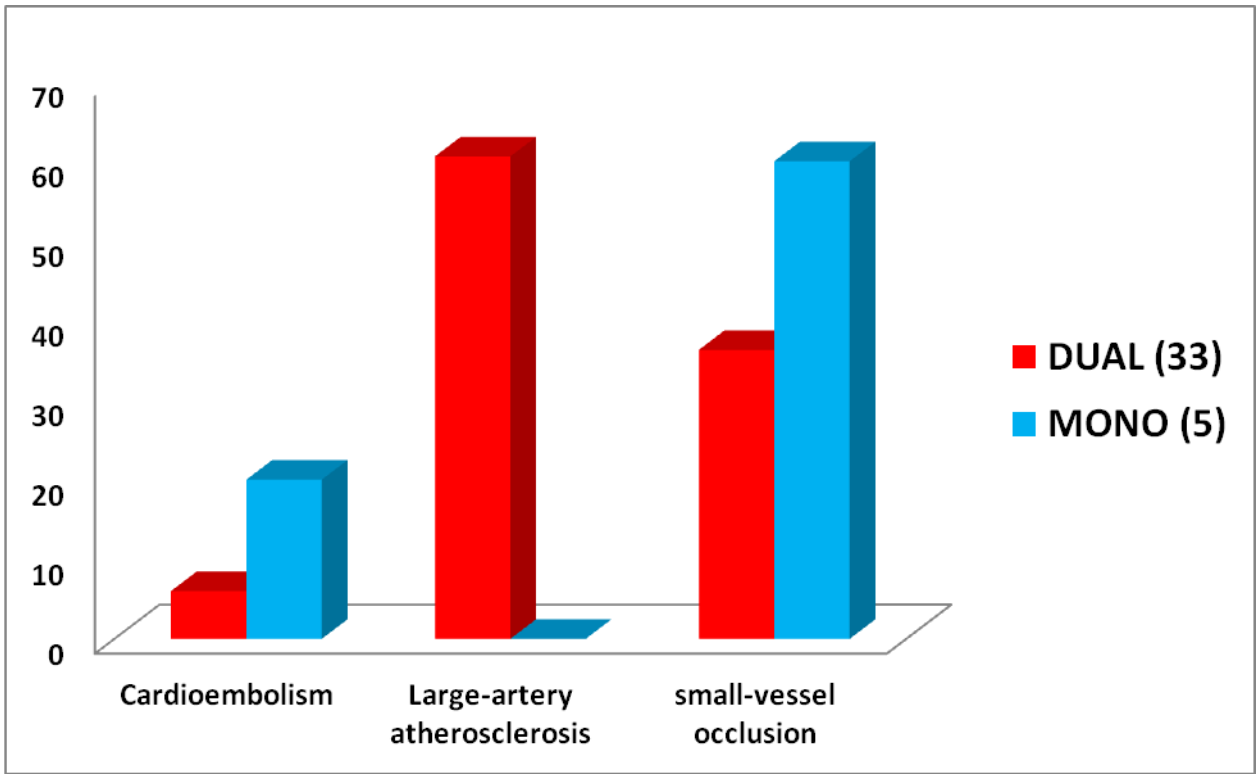


TABLE 6: Baseline characteristics of the study population.

Data are expressed as number (%) or mean ± SD

	DUAL (n=33)	MONO (n=5)
MEAN AGE (years ± S.D)	**60.93 ± 11.45**	**64.2 ± 20.64**
QUALIFYING EVENT		
IS	**31(93.9)**	**5(1)**
TIA	**2(6)**	**0**
TOAST CLASSIFICATION		
Cardioembolism	**2(6)**	**1(20)**
Large-artery atherosclerosis	**20(60.6)**	**0**
Small-vessel occlusion	**12(36.3)**	**3(60)**
Stroke of other determined cause	**-**	**-**
Undetermined cause	**-**	**-**
RISK FACTORS AND MEDICAL HISTORY		
Previous IS (before qualifying event)	**12(36.3)**	**1(20)**
Hypertension	**30(90.9)**	**3(60)**
Diabetes	**16(48.4)**	**4(80)**
Hypercholesterolaemia	**19(57.5)**	**4(80)**
Past or current smoker	**11(33.3)**	**2(40)**

FIGURE 6: Characterization of the study population according to the TOAST CLASSIFICATION



TOAST CLASSIFICATION

FIGURE 7 : Characterization of the study population on the basis of Risk factors and medical history

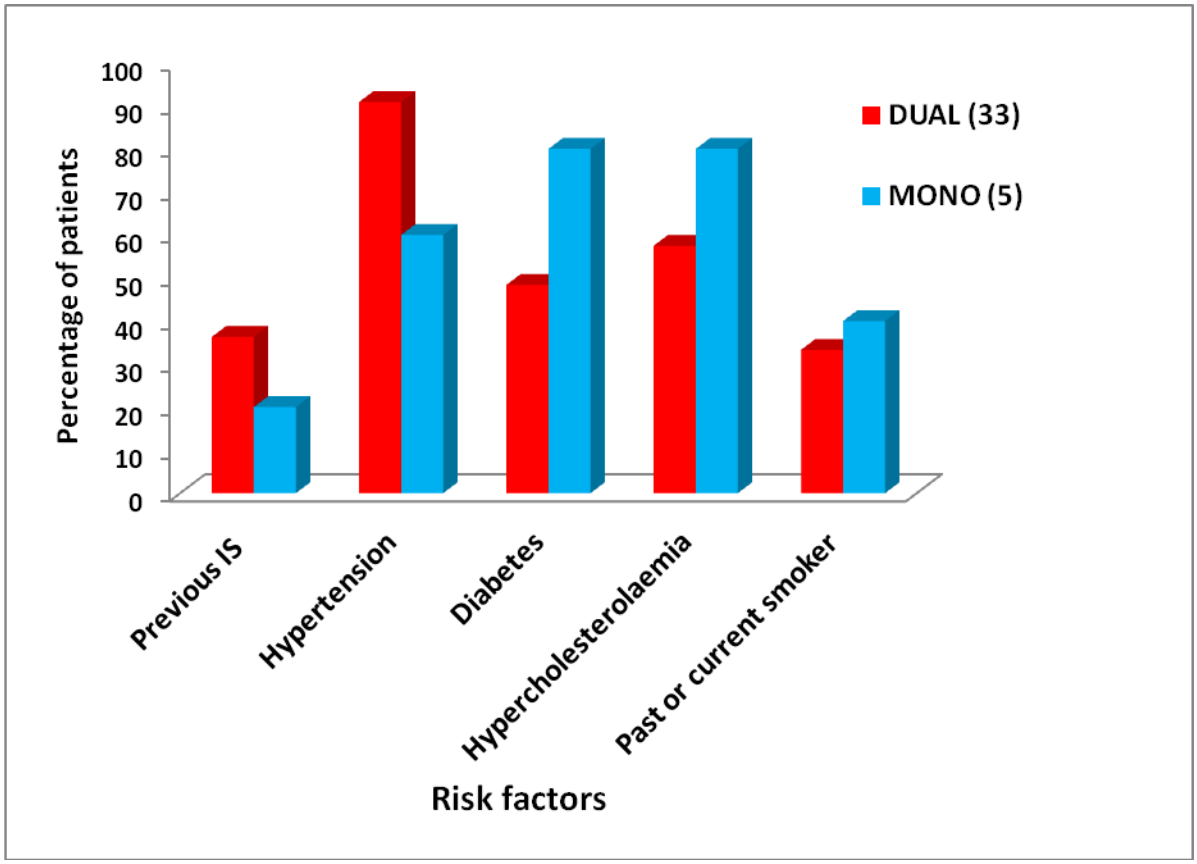
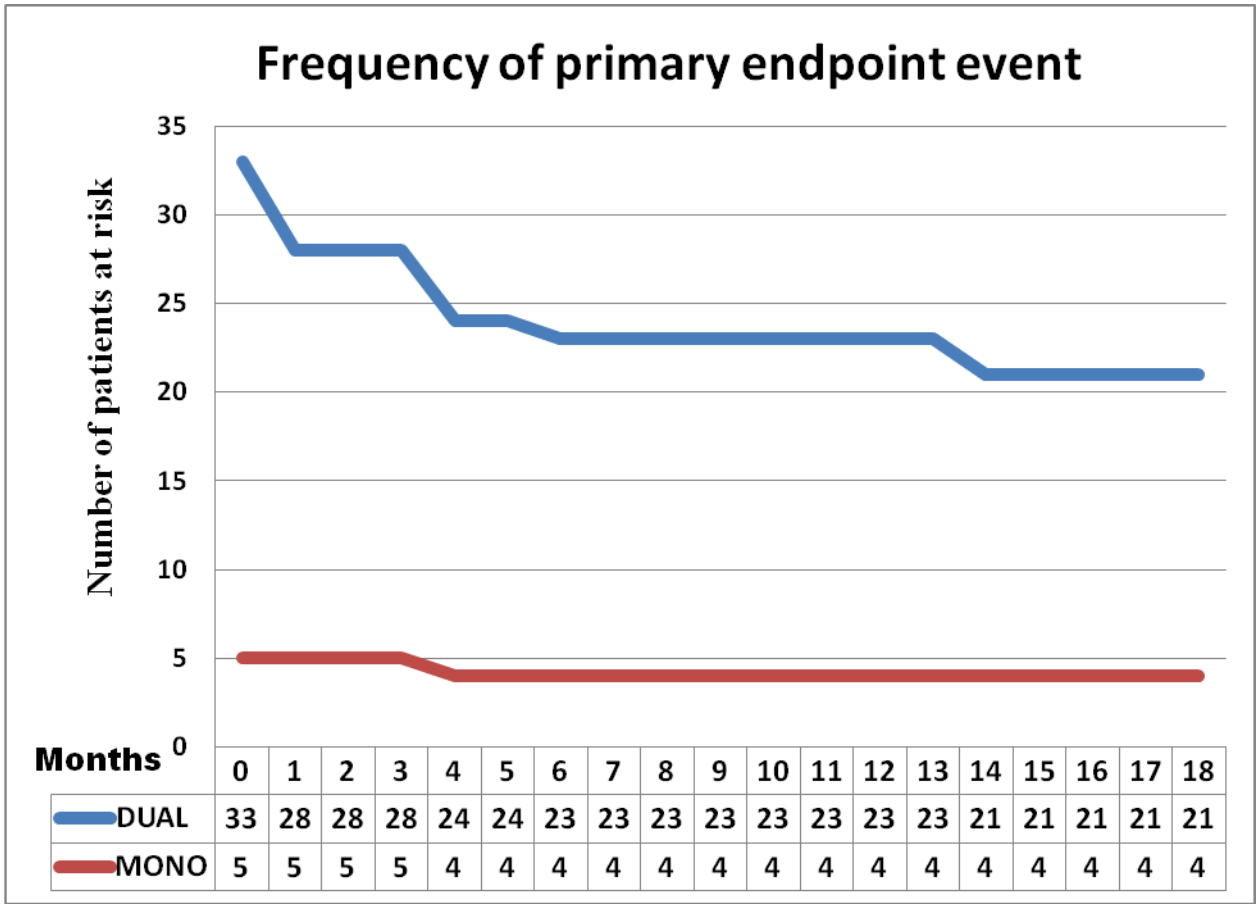


FIGURE 8 : Frequency of primary endpoint event



Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
DUAL	33	28	28	28	24	24	23	23	23	23	23	23	23	23	21	21	21	21	21
MONO	5	5	5	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

TABLE 7 : Rates of primary endpoint event in specified subgroups

Subgroup			EVENT RATE (%)	
		number(n)	DUAL	MONO
Qualifying event	IS	36	35.48	0.2
	TIA	2	0.5	0
Age(years)	<61	18	31.2	0
	≥61	20	41.1	33.3
Sex	Female	8	14.2	0
	Male	30	42.3	0.25
Hypertension	No	5	0	0
	Yes	33	0.4	33.3
Diabetes	No	18	47	0
	Yes	20	0.25	0.25
Previous IS	No	25	0	0
	Yes	13	1	1

TABLE 8 :Univariate analysis of factors affecting primary event

Subgroup		Recurrence	Non recurrence	P value
Age < 61		8	15	< 0.20
Age ≥ 61		5	10	
Male		12	18	< 0.01
Female		1	7	
Hypertension	YES	13	20	< 0.01
	NO	0	5	
Previous IS	YES	13	0	< 0.01
	NO	0	25	
Diabetes	YES	5	11	< 0.7
	NO	8	10	
Therapy	MONO	1	4	< 0.01
	DUAL	12	21	

TABLE 9 : Relative risk of primary endpoint in different subgroups on dual and mono antiplatelet therapy.

Subgroup	Relative risk	95% CI	P value
Ischaemic stroke	1.7742	0.2886 -10.9086	0.5361
TIA	1.0000	0.104 - 9.6139	1.0000
Age < 61	1.9412	0.141 - 26.7183	0.6200
Age ≥ 61	1.2353	0.2261 - 6.7498	0.8073
Male	1.6923	0.2924 - 9.7948	0.5570
Female	0.7500	0.04558 - 12.3407	0.8404
Hypertension	0.9744	0.41 - 2.3153	0.9531
Previous IS	1.2821	0.5717 - 2.8748	0.5465
Diabetes	1.0000	0.1499 - 6.6709	1.0000

Discussion

DISCUSSION

Stroke is an enormous and serious public health problem. Not only is it a common cause of death but also it is a major cause of disabilty among adults. Approximately, 20 million people suffer from stroke each year and out of these 5 million do not survive. Developing countries account for 85% of global deaths from stroke. Stroke causes functional impairments, 20% survivors require institutional care after 3 months and disability occurs in 15-30% **(Balucani, et al., 2010).** Ischemic stroke is found to be the principal universal cause of disability in the developed world, and the third leading cause of mortality. It is expected that 8–12% of individuals are found to die within the first 30 days of their initial stroke, and patients who survive the initial attack face an enlarged risk of successive vascular events and stroke, as approximately one-quarter of all strokes occurring each year are found to be recurrent. 21.5% of patients are found to be experiencing either a recurrent stroke or a transient ischemic attack (TIA) within the first year following the initial attack **(Diener and Wong, 2008).** Our results showed that out of the total patients, 34.2% had recurrence of vascular events.

Official census data from the United Kingdom in 1981, 1991, and 2001 have persistently shown inequalities in ischemic stroke mortality among the South Asian population. According to the 3 cross-sectional studies based on the national census data in the United Kingdom, the average standard mortality ratios (SMR) in South Asians were 55% and 41% higher in males and females, respectively when compared with the white population **(Gunarathne, et al., 2009).**

In a Prospective Community-Based Study of Stroke in Kolkata, India **(Das, et al., 2007)**, Out of the screened population of 52 377 (27 626 men, 24 751 women), the age standardized prevalence rate of stroke to world standard population was 545.10 (95% CI, 479.86 to 617.05) per 100 000 persons. The age standardized average annual incidence rate to world standard population of first-ever-in-a-lifetime stroke was 145.30 (95% CI, 120.39 to 174.74) per 100 000 persons per year. Thirty-day case fatality rate was 41.08% (95% CI, 30.66 to 53.80). Women had higher incidence and case fatality rates.

In our study the age of the study population varied from 41 to 90 years and the mean age of the study population was found to be 61.36 years. In the population identified, the number of male patients were found to be 78.94% and female patients were 21 %.

A randomized, double-blind, placebo-controlled trial revealed that the most prevalent risk factors at randomization were hypertension (78%), diabetes mellitus(68%) and hypercholesterolemia (56%). 26% of patients had previous ischemic stroke and 19% had transient ischemic attack. Most patients had one additional risk factor, as defined in the inclusion criteria at study entry, and 20% had two or more **(Diener, et al.,2004).** In our total study population, 86.8 % were having hypertension as the risk factor, 52.6% patients were identified to be having diabetes and 34.2 % of patients had a previous history of stroke. Previous ischemic stroke, hypertension, diabetes, hypercholesterolemia were found to be the most common risk factors in the population studied. Previous ischemic stroke was reported in 12 % of dual therapy group and 1% in the mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was found to be a risk factor in 16% of dual therapy patients and 4% in monogroup. Hypercholesterolemia was identified as risk factor in 19% of dual group and 4 % of mono group.11% of dual therapy patients and 2 % of mono therapy patients were smokers.

The only South Asian studies **(Syed, et al., 2003)** that classified their stroke population according to the TOAST taxonomy found a higher prevalence of lacunar strokes (42.7% and 68%) compared with large vessel infarctions (26% and 10%). In our study, according to TOAST classification, majority of the patients were found to have large artery atherothrombosis **(Gunarathne, et al., 2009).**

Of the 700,000 strokes that occur yearly in the United States, 200,000 are recurrent events. The risk of recurrent stroke has been reported as 11.5% at 7 days, 6% to 15% at 30 days, and 18.5% at 3 months. Following a transient ischemic attack (TIA), the estimated risk of recurrent stroke was 8% at 7 days, 11.5% at 1 month, and 17.3% at 3 months. However, in our study, out of the total study population, 36 patients had ischemic stroke as the qualifying event and 2 patients were having Transient Ischemic Attack. The event rate for ischemic stroke in dual therapy group was found to be 35.48 % and 0.2% for TIA. The event rate for TIA was found to be 0.5 % in dual group **(Kiwon, et al., 2007).**

In a MATCH trial conducted in 507 centres, the event rates for the primary endpoint in different predefined patient subgroups indicated a slight favour for adding aspirin to clopidogrel compared with placebo to clopidogrel in most subgroups. No interactions were reported between covariates and treatment effect, apart from patient age and treatment effect **(Diener, et al., 2004).** In our study, the relative risk for recurrence were obtained from the study population and our results indicate a favour for monotherapy (clopidogrel alone) compared to dual (clopidogrel + aspirin). In patients having ischemic stroke the relative risk of dualtherapy was found to be 1.7742 times than that of dual therapy. The relative risk was found to be the same for both mono and dual therapy in patients having TIA. Relative risk with dual therapy was 0.9412 times than dual therapy in patients of age < 61years and 1.2353

times in age ≥ 61 years. In male patients, relative risk with dualtherapy was 1.6923 times than that with mono therapy and in females it was found to be 0.7500 times that of mono. Patients with hypertension had 0.9744 times the risk and those with previous ischemic stroke had 1.2821 times risk than with mono therapy. The relative risk in patients having diabetes was found to equal in both dual and mono therapy.

Conclusion

CONCLUSION

The aim of the study was to determine whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in the prevention of secondary vascular events in patients after TIA or ischemic stroke. Out of the total patients, 34.2 % of patients had recurrence of vascular events. 36.3 % patients reached the primary endpoint in the group receiving dual therapy compared to 20% in the monotherapy group. 31% in dual therapy group had Ischemic stroke as qualifying event compared to 5 % in monotherapy.

Our study focused on the prevalence of risk factors in patients with recurrence of vascular events. Risk factors found were previous ischemic stroke in 12 % of dual therapy group and 1% in mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was risk factor in 16% of dual therapy patients and 4% in monogroup Hypercholesterolemia was found in 19% of dual group and 4 % of mono group11% of dual therapy patients and 2 % of mono therapy patients were smokers.

In our study, we also observed the prescribing trends in patients, and noted that dual therapy was found to be more prominent than monotherapy. Dual therapy did not appear to have any added advantage over monotherapy as the event rate of recurrence of vascular event were more in patients under dual therapy. The primary events were found to have a significant association with gender, risk factors and therapy. No bleeding complications were observed in the study population.

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Annexures

KMCH ETHICS COMMITTEE

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✆ : (0422) 4323800 Fax : Fax : (0422) 4270805

Ref: EC/AP/163/10/2011
24.10.2011

APPROVED

To

Dr.Suchandra Sen, M.Pharm, PhD
Department of Pharmacy Practice,
KMCH College of Pharmacy,
Coimbatore-641048
Tamilnadu, India.

Dear Dr. Suchandra Sen,

The proposal entitled "**A study on the effectiveness of mono and dual antiplatelet therapy in secondary prevention of vascular events**" submitted by Mr.Fazil Babu K.P was reviewed by the Ethics Committee in its meeting held on 22.10.2011 and permission is granted to you to carryout the study at Kovai Medical Center and Hospital Ltd, Coimbatore, India.

Thanking you,

Yours faithfully,

24/10/'11

Dr. P. R. Muthuswamy
Chairman, Ethics Committee

Dr. P. R. MUTHUSWAMY,
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Dr. K. VIJAYAN M.D., DNB., DM (NEURO)
Consultant Neurologist

Reg. No. 54013
Cell : 98421 - 55101

CERTIFICATE

This is to certify that the research work entitled "**A STUDY ON THE EFFECTIVENESS OF MONO AND DUAL ANTIPLATELET THERAPY IN SECONDARY PREVENTION OF VASCULAR EVENTS**" carried out by **Mr. Fazil Babu. K.P (26107281)** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment for the degree of Master of Pharmacy in Pharmacy Practice is a bonafide work carried out by the candidate under my supervision at the Department of Neurology, Kovai Medical Center and Hospital, Coimbatore during the academic year of 2011 – 2012.

DR. K.VIJAYAN, M.D., DNB., DM (NEURO)
Consultant Neurologist
Kovai Medical Center and Hospital, Coimbatore

Dr. K. VIJAYAN, MD;DNB;DM (Neuro)
Reg. No: 54013
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COIMBATORE - 14.

DATA ENTRY FORM

Name of Patient:

……

Date of admission …… / …… /…… **Time** …… **IP No:** ……..

Address:…….....

Contact number: ...……

Age in years : **30-50** ☐ **50-70** ☐ **70-90** ☐

Sex : **M** ☐ **F** ☐

Occupation: **None** ☐ **Housewife** ☐ **Agriculture** ☐ **Business** ☐

Govt employee ☐ **Student** ☐ **Other** ☐ **Unknown** ☐

Family income: **upto 60,000** ☐ **60,000-1,80000** ☐ **1,80000 and above** ☐

Antiplatelet therapy prescribed: **Clopidogrel** ☐ **Clopidogrel+Aspirin** ☐

Brands and dose of antiplatelets: ……

Stroke subtype: **Ischemic** ☐ **Embolic** ☐

Recurrence of Stroke : **YES** ☐ **NO** ☐

If yes, fill the following:

No. of recurrences: **Nil** ☐ **1** ☐ **2** ☐ **3 and above** ☐

Frequency of recurrence during treatment ……..

……

Risk factors : **Hypertension** ☐ **Diabetes mellitus** ☐ **Smoking** ☐

Alcoholism ☐ **Cardiac diseases** ☐

Dyslipidemias ☐

Duration of treatment : **1-2 years** ☐ **3-4 years** ☐ **above 5 years** ☐